Introduction

The number of patients with type 2 diabetes has been increasing worldwide over the past few decades, and is now a serious global health burden. Type 2 diabetes causes hyperglycemia due to impaired insulin secretion and/or insulin resistance, resulting in glucotoxicity in various organs, which leads to severe complications including cardiovascular diseases, nephropathy, retinopathy, and peripheral neuropathy (1). Thus, patients with type 2 diabetes have been treated with insulin or insulin secretagogues such as sulfonylureas, glinides, dipeptidyl-peptidase IV (DPP-IV) inhibitors, and glucagon-like peptide-1 (GLP-1) analogues or insulin sensitizers such as metformin and glitazones to normalize hyperglycemia (2, 3). Although sulfonylureas and glinides effectively lower plasma glucose by stimulating insulin release from pancreatic beta cells, they may cause critical hypoglycemia (2). DPP-IV inhibitors and GLP-1 analogues stimulate insulin release in a glucose-dependent manner; therefore, they have been used as safer insulin-secretagogues (3, 4). Insulin sensitizers are effective...
in reducing plasma glucose without an increase in plasma insulin levels in type 2 diabetic patients with insulin resistance and hyperinsulinemia. However, only metformin and two glitazones are clinically used as insulin sensitizers. Metformin has been used for a long time, but has moderate efficacy and may cause lactic acidosis (5, 6). Although glitazones such as rosiglitazone and pioglitazone, peroxisome proliferator-activated receptor (PPAR) γ agonists, have been used as effective insulin sensitizers, they have adverse effects such as fluid retention, hemodilution, body weight gain, hepatotoxicity, the risk of heart failure, and reductions in bone mineral density (BMD) (7, 8). Thus, a large number of PPARγ or PPARα/γ agonists have been synthesized to find a safer and more efficacious insulin sensitizer; however, none have been successfully developed to date (9).

The novel PPARα/γ agonist (S)-7-(2-{2-[{(E)-2-cyclopentylvinyl]-5-methyloxazol-4-yl}ethoxy}-2-[(2E,4E)-hexadienyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (KY-201, Fig. 1) was reported to exhibit protein tyrosine phosphatase-1B (PTP1B) inhibitory activity (10). PTP1B is known as a non-receptor type tyrosine phosphatase and negatively regulates insulin and leptin signaling (11, 12). The genetic deletion or pharmacological intervention of PTP1B is known to have anti-diabetic and anti-obesity effects by amplifying insulin and leptin signaling, respectively (13, 14). KY-201 was previously reported to reduce plasma glucose and triglyceride (TG) levels more effectively than rosiglitazone in KK-A^y^ mice, even though both compounds have similar human PPARγ agonistic activities in COS-1 cells (10), which suggests the involvement of PTP1B inhibition in its insulin-sensitizing effects. PPARγ-related adverse effects such as fluid retention and hepatomegaly were weaker with KY-201 than with rosiglitazone in normoglycemic mice (10). However, its safety for cardiac hypertrophy, obesity, and reductions in BMD, all PPARγ-related adverse effects, remains to be determined.

In the present study, the hypolipidemic effects and adverse effects of KY-201, including fluid retention, cardiac hypertrophy, obesity, and reductions in BMD, were compared with those of rosiglitazone, a PPARγ full agonist, in ovariectomized (OVX) female rats, which are used widely as an experimental osteoporosis model with normoglycemia, insulin resistance, mild obesity, and hyperlipidemia (15).

**Materials and Methods**

**Materials and animals**

KY-201, rosiglitazone, and ertiprotafib were synthesized in our laboratories. ST-2 cells and HepG2 cells were purchased from Rikagaku Kenkyusho (Tsukuba) and Dainippon Sumitomo Pharma Co., Ltd. (Osaka), respectively. Roswell Park Memorial Institute (RPMI)-1640 medium and Dulbecco’s modified Eagle’s medium (DMEM, Nissui Pharmaceutical, Co., Ltd., Tokyo) or alpha Modified Eagle Minimum Essential Medium (α-MEM; Life Technologies, Inc., Carlsbad, CA, USA) that contained 10% fetal bovine serum (JRH Bioscience, Inc., Lenexa, KS, USA), 0.3% NaHCO_3, and 1% penicillin-streptomycin were used for the cell culture. The anti-phosphorylated insulin receptor, anti-insulin receptor, and peroxidase-conjugated antibody were purchased from Merck Millipore (Billerica, MA, USA), Santa Cruz (Dallas, TX, USA) and Cell Signaling Technology, Inc. (Danvers, MA, USA), respectively. Female F344/NSlc rats were purchased from Japan SLC, Inc. (Hamamatsu) and individually housed under conditions with controlled temperature, humidity, and light exposure (12 h light–dark cycle) and were allowed ad libitum access to commercial standard rodent chow (CE-2; CLEA Japan, Inc., Tokyo) and tap water. Animals were handled in accordance with the “Guidelines for Animal Experimentation” approved by The Japanese Pharmacological Society, and all procedures were approved by the Animal Ethical Committee of Kyoto Pharmaceutical Industries. KY-201, rosiglitazone, and ertiprotafib were dissolved in dimethyl sulfoxide (DMSO; Nacalai Tesque, Kyoto); each drug solution was diluted in buffer or medium for in vitro study or suspended in 0.5% methylcellulose (Nacalai Tesque) for oral administration to animals.

**OVX rats and treatment**

Eight-week-old female F344/NSlc rats were anesthetized using ketamine (37.5 mg/kg, i.p.) and xylazine (7.5 mg/kg, i.p.), and bilateral ovariectomy was performed. Two days after surgery, OVX rats were randomized into 5 groups: vehicle-treated group and KY-201- and rosiglitazone-treated groups at 3 and 10 mg/kg per day. A sham-operated group and satellite group for a pharmacokinetic study were also used. Rats were orally administered vehicle or drugs for 6 weeks and then deeply

![Fig. 1. Chemical structure of KY-201.](image-url)
Each maximal activity was taken as 100% and median (PicaGene LT7.5; TOYO B-Net CO., Ltd., Tokyo). Activities were determined using a commercial kit presence or absence of the test compound. Luciferase of 1.5 × 10^5 Cells were then seeded in 96-well plates at a density Nucleofector II (AAD-1001S; Lonza, Basel, Switzerland). tk-luc were electroporated into ST-2 cells using MD, USA) with the reporter plasmid pGL3-PPREx4-human RXR (Open Biosystems, Inc, Huntsville, AL, USA) and full-length mouse PPAR (Technologies, Inc.) according to the manufacturer's instructions. PPARγ2, CCAAT/enhancer-binding protein alpha (C/EBPα), GPDH, lipoprotein lipase, adipocyte protein 2, and adiponectin mRNAs were determined by real-time polymerase chain reaction (real-time PCR).

**PPARγ agonist activity**

ST-2 cells were cultured in RPMI1640 under 5% CO₂ at 37°C. The full-length mouse PPARγ 1 plasmid (Open Biosystems, Inc, Huntsville, AL, USA) and human RXRα plasmid (GeneCopoeia, Inc., Rockville, MD, USA) with the reporter plasmid pGL3-PPREx4-tk-luc were electroporated into ST-2 cells using Nucleofector II (AAD-1001S; Lonza, Basel, Switzerland). Cells were then seeded in 96-well plates at a density of 1.5 × 10^4 cells/well and incubated for 24 h in the presence or absence of the test compound. Luciferase activities were determined using a commercial kit (PicaGene LT7.5; TOYO B-Net CO., Ltd., Tokyo). Each maximal activity was taken as 100% and median effective concentration (EC₅₀) values were calculated.

Isolation of rat bone marrow-derived mesenchymal stem cells (BMSCs)

Bone marrow-derived mesenchymal stem cells were isolated from eight-week-old female F344/NSle rats. Animals were deeply anesthetized with pentobarbital sodium (50 mg/kg, i.p.) and bled to death. The femoral bones were isolated and placed in fresh phosphate-buffered saline (PBS, pH 7.4) containing 1% penicillin-streptomycin. The bones were then cut at the ends and flushed with α-MEM. After centrifugation, the precipitated cells were resuspended in α-MEM and plated in 10-cm dishes at 5% CO₂ and 37°C. Adherent cells were then cultured for 1 week and used as BMSCs.

**In vitro osteoblast differentiation in rat BMSCs**

BMSCs were seeded in 96-well plates at a density of 4 × 10^3 cells/well. Test compounds were added 24 h later and cultured for 4 days. Cells were then washed with PBS (pH 7.4) and lysed in 50 μL saline containing 1% NP-40. The reaction was started by the addition of 50 μL of 10 mM p-nitrophenol phosphate in 50 mM ethanol amine and stopped by the addition of 50 μL of 1 N NaOH after 30 min incubation at 37°C. Alkaline phosphatase (ALP) activities were determined by measuring the absorbance at 405 nm.

**In vitro adipocyte differentiation**

BMSCs were seeded in 96-well plates at a density of 4 × 10^3 cells/well. Test compounds were added 24 h later and cultured for 4 days. Glycerol-3-phosphate dehydrogenase (GPDH) activities were measured using a commercial GPDH assay kit (Primary Cell Co., Ltd., Sapporo). BMSCs were seeded separately in 6-well plates at a density of 8 × 10^4 cells/well, and cultured for 4 days. Total RNA was prepared using Trizol (Life Technologies, Inc.) according to the manufacturer’s instructions. PPARγ2, C/EBPα, GPDH, lipoprotein lipase, adipocyte protein 2, and adiponectin mRNAs were determined by real-time polymerase chain reaction (real-time PCR).

**Real-time PCR**

To synthesize cDNAs, 0.1 μg total RNAs were reverse-transcribed using a commercial kit (Cosmo Bio Co., Ltd., Tokyo). The reaction was performed under the following conditions: synthesis at 37°C for 15 min and heat inactivation of reverse transcriptase at 85°C for 1 min. cDNAs were then stored at −30°C until use. Real-time PCRs were performed in 10 μL of the total reaction volume containing 5 μL of cDNAs, individual primer pairs, a fluorescently-labeled probe, and the commercial reagent (Light Cycler 480 Probes Master; Roche Diagnostics, Tokyo) according to the manufacturer’s
PTP1B inhibitory activity

PTP1B inhibitory activities were determined in the absence or presence of the test compounds in 100 μL of 100 mM 4-(2-hydroxyethyl)-1-piperazinethesulfonic acid (HEPES) buffer (pH 7.2) containing a human PTP1B enzyme (Enzo Life Sciences, Inc., Farmingdale, NY, USA), 3 mM p-nitrophenol phosphate, 1 mM dithiothreitol, 1 mM ethylenediaminetetraacetic acid (EDTA), and 0.001% Triton-X. The reaction was started by the addition of p-nitrophenol phosphate and stopped by the addition of 50 μL of 1N NaOH after 10 min incubation at 37°C, and absorbance was determined at 405 nm. The DMSO-treated enzymatic activity level was taken as 100%, and 50% inhibitory concentration (IC50) was calculated.

Insulin receptor phosphorylation in HepG2 cells

HepG2 cells suspended in DMEM were seeded in 6-well plates at a density of 1 × 10⁶ cells/well and cultured under 5% CO₂ at 37°C for 24 h and then for 6 h in serum-free DMEM. Cells were cultured in the presence or absence of test compounds for 1 h, followed by incubation with 1 nM insulin for 10 min. Cells were washed with 20 mM Tris-HCl buffer (pH 7.5) containing 5 mM EDTA-2Na, 10 mM sodium fluoride, 10 mM sodium β-glycerophosphate, 10 mM Na₂PO₄, and 10 mM NaVO₃; harvested; and suspended in 20 mM Tris-HCl buffer (pH 7.5) with 1 μg/mL p-amidinophenyl methanesulfonyl fluoride, leupeptin, 1 μg/mL antipain, 1 μg/mL benzamidine, and 1% Triton X-100. The suspensions were added at a volume of 4:1 to 50 mM tris(hydroxymethyl)aminomethane (Tris)-HCl buffer (pH 6.8) containing 10% sodium dodecylsulfate, 0.05% bromophenol blue, 50% glycerol, and 25% mercaptoethanol followed by heating and mixing at 100°C for 10 min. Each 30 μg aliquot of protein was loaded on a 7.5% polyacrylamide gel for electrophoresis at a constant current of 30 mA/plate for 1 h, followed by blotting to a polyvinylidene difluoride (PVDF) membrane previously treated with 100% methanol. After blocking by 10% skim milk dissolved in 20 mM Tris-HCl buffer (pH 7.5) containing 0.05% Tween 20 and 137 mM NaCl (TBS-T) for 1 h, the membrane was incubated with the anti-phosphorylated insulin receptor antibody or anti-insulin receptor monoclonal antibody diluted in TBS-T containing 1% skim milk (1:1000) followed by incubation with a peroxidase-conjugated antibody (1:1000). The protein content was determined using a chemiluminescence reagent (Chemi-Lumi One Super; Nacalai Tesque) and Chem Doc and Image Lab software (BioRad Laboratories, Inc., Hercules, CA, USA).

Statistical analyses

All data are expressed as the mean ± S.E.M. The significance of differences was assessed by a two-tailed student’s t-test for paired data for in vitro assays and by Dunnett’s multiple comparison test for in vivo assays.

Results

Effects of KY-201 and rosiglitazone in OVX rats

The insulin sensitizing effects of KY-201 were previously shown to be 10 times stronger than those of rosiglitazone in KK-A⁻ mice, despite its lower PPARγ activity and plasma concentration. In this study, hypolipidemic effects and adverse effects were investigated in OVX rats. Ovariectomy increased body weight gain, serum TG, and serum NEFA levels to a similar extent (Table 1). Ovariectomy increased adipose tissue weight, heart weight, and blood volume, whereas KY-201 at both doses did not. The plasma maximal concentrations of KY-201 and rosiglitazone after their final administration were 0.54 and 6.17 μg/mL (1.1 and 12.5 μM, n = 2), respectively, at 3 mg/kg per day, and they were 3.56 and 17.99 μg/mL (10.0 and 50.3 μM, n = 2), respectively, at 10 mg/kg per day. Ovariectomy significantly decreased the BMDs of lumbar vertebra and femurs. Rosiglitazone...
significantly decreased the BMD of lumbar vertebra at 10 mg/kg per day, while KY-201 did not (Fig. 3A). KY-201 at 10 mg/kg per day and rosiglitazone at both 3 and 10 mg/kg per day significantly decreased the BMD of the femur (Fig. 3B). On hematoxylin and eosin staining analysis of sections, rosiglitazone more apparently increased fat in bone marrow cavity than KY-201 in femurs (Fig. 4A). Ovariectomy increased fat in the marrow cavity by 10%. Rosiglitazone further increased fat in the marrow cavity by 17% at 3 mg/kg per day and significantly increased it by 27% at 10 mg/kg per day, whereas KY-201 had no effect (Fig. 4B).

**PPARγ agonist activities**

The transactivation of PPARγ was investigated using a luciferase reporter assay. KY-201 and rosiglitazone at $10^{-7} - 10^{-5}$ M activated mouse PPARγ in a concentration-dependent manner. KY-201 was 2 times weaker than rosiglitazone (EC$_{50}$: 287 ± 88 and 148 ± 39 nM, respectively). The maximal activation level by KY-201 was 54.1% ± 1.1% that of rosiglitazone (Fig. 5).

### Effects on osteoblast and adipocyte differentiation in BMSCs

In rat BMSCs, rosiglitazone significantly decreased ALP activities from $10^{-9}$ M in a concentration-dependent manner, while KY-201 significantly decreased it from $10^{-7}$ M. The reducing effects of KY-201 were significantly weaker than those of rosiglitazone at $10^{-8} - 10^{-5}$ M (Fig. 6A). KY-201 and rosiglitazone significantly increased GPDH activities from $10^{-7}$ M in a concentration-dependent manner, although the effects of KY-201

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### Table 1. Body weight gain and levels of serum glucose, TG, and NEFA in OVX rats treated with KY-201 and rosiglitazone

<table>
<thead>
<tr>
<th></th>
<th>Sham operated</th>
<th>Control</th>
<th>KY-201 (mg/kg per day)</th>
<th>Rosiglitazone (mg/kg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Body weight gain (g)</td>
<td>45.9 ± 2.4**</td>
<td>70.4 ± 3.0</td>
<td>72.4 ± 3.4</td>
<td>72.4 ± 3.4</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>146 ± 9</td>
<td>153 ± 4</td>
<td>163 ± 8</td>
<td>146 ± 4</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>38 ± 6</td>
<td>46 ± 10</td>
<td>28 ± 5</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>NEFA (mEq/L)</td>
<td>0.50 ± 0.02</td>
<td>0.61 ± 0.03</td>
<td>0.54 ± 0.03**</td>
<td>0.43 ± 0.02**</td>
</tr>
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The values are the mean ± S.E.M. (n = 8). *P < 0.05 and **P < 0.01 vs. the Control group.
were significantly weaker than those of rosiglitazone at $10^{-6}$ M and $10^{-5}$ M (Fig. 6B).

**Effects on adipogenic gene expression in BMSCs**

The effects of KY-201 and rosiglitazone on adipocyte marker genes expression were examined in BMSCs. KY-201 and rosiglitazone increased the expression levels of genes involved in adipocyte differentiation: PPARγ, cEBPα, GPDH, lipoprotein lipase, adipocyte protein 2, and adiponectin, in a concentration-dependent manner. Although the effects of both drugs were similar at $10^{-9} – 10^{-7}$ M, the effects of KY-201 at higher than $10^{-7}$ M were weaker than that of rosiglitazone; increases in expression levels by KY-201 at $10^{-6}$ and $10^{-5}$ M were approximately 30% – 80% those of rosiglitazone (Fig. 7).

**Effects on PTP1B activity and insulin receptor phosphorylation**

KY-201 and ertiprotifib, a PTP1B inhibitor (16), inhibited PTP1B activity in a concentration-dependent manner, whereas rosiglitazone did not. The IC_{50} values of KY-201 and ertiprotifib were 3.7 ± 1.0 and 0.64 ± 0.24 μM, respectively (Fig. 8A). The insulin sensitizing effect of KY-201 was examined in a cell-based phos-
Discussion

The present study was undertaken to determine whether KY-201 showed hypolipidemic effects with less adverse effects than rosiglitazone in OVX rats, and, if any, to clarify their mechanisms. OVX rats are an experimental model for osteoporosis in postmenopausal woman, which shows a marked reduction in BMD, obesity, and hyperlipidemia, but not hyperglycemia (15, 17). TG and NEFA, but not glucose levels were slightly increased by ovariectomy, and these increased TG and NEFA levels were similarly reduced by KY-201 and rosiglitazone. Insulin is known to lower plasma TG and NEFA levels by inhibiting very-low-density lipoprotein (VLDL) secretion from hepatocytes and uptake into adipocytes via lipoprotein lipase activation (18, 19). PPARγ agonists have been shown to reduce TG and NEFA levels by insulin sensitization in diabetic rats (20). However, KY-201 was found to exhibit partial human PPARγ agonistic activity in COS-1 cells (10),
and its plasma concentrations in OVX rats were approximately 10 times lower than those of rosiglitazone. Thus, the effects of KY-201 appear to be attributed, at least in part, to activity other than PPARγ agonistic activity. KY-201, but not rosiglitazone, inhibited PTP1B and increased insulin-stimulated insulin receptor phosphorylation in HepG2 cells. PTP1B is known to negatively regulate the insulin signal by dephosphorylating the insulin receptor and insulin receptor substrate phosphorylated by insulin (11). The overexpression of PTP1B in muscle has been proposed to cause insulin resistance (21). Hepatic deletion and PTP1B inhibitors were shown to improve insulin resistance and reduce plasma glucose and TG levels in diabetic mice (14, 22). The plasma concentrations of KY-201 in OVX rats were compatible with PTP1B inhibitory concentrations. It is likely that KY-201 showed hypolipidemic effects by partial PPARγ activation and PTP1B inhibition, the effects of which were similar to those of rosiglitazone by full PPARγ activation. Similar phenomena were observed in normoglycemic Zucker fatty rats with insulin resistance. KY-201 and rosiglitazone showed similar reducing effects on TG and NEFA levels and on elevated glucose levels in a glucose tolerance test (unpublished data). On the other hand, PTP1B inhibition was considered to more effectively exert insulin-sensitizing effects in diabetic mice; the hypoglycemic and hypolipidemic effects of KY-201 were approximately 10 times stronger than those of rosiglitazone, although its PPARγ activation levels and plasma concentrations were lower (10). However, the reason why the plasma maximal concentration of KY-201 was lower than that of rosiglitazone is not clarified so far. Differences in molecular weights and/or acidic moieties could affect the plasma maximal concentrations.

Only a high dose of rosiglitazone significantly increased body weight gain, adipose tissue weight, blood volume, and heart weight in OVX rats, which are all considered to be PPARγ-mediated adverse effects. PPARγ agonists promote adipocyte differentiation from preadipocytes in abdominal and subcutaneous adipose tissue, resulting in adiposity (23). PPARγ agonist–induced fluid retention is attributed to the activation of epithelial Na⁺ channel subunit gamma in the collecting duct and/or to Na⁺, K⁺ATPase activation via proximal tubular PPARγ (24). The cardiac hypertrophy caused by PPARγ agonists appears to be induced by increased cardiac preload through fluid retention and/or cardiomyotic PPARγ activation (25, 26). The increase in body weight gain may be due to adiposity and/or fluid retention. CT analyses demonstrated that ovariectomy reduced BMD in lumbar vertebra and femurs. BMDs in these regions were markedly lower due to the rosiglitazone treatment than the KY-201 treatment. Insulin promotes osteoblastogenesis (27) and type 2 diabetic patients are at higher risk of bone fractures (8). PPARγ agonists are more likely to increase the risk of bone fractures in diabetic patients. Rosiglitazone and pioglitazone have been reported to increase the risk of bone fracture by decreasing BMDs in aged women (2, 8), which is explained by a shift from osteoblast differentiation to adipocyte differentiation by PPARγ activation in BMSCs (28, 29). Rosiglitazone, but not KY-201 markedly increased fat in the bone marrow cavity in OVX rats.

KY-201 has weaker adverse effects than rosiglitazone and this is considered to be due to its weaker PPARγ agonistic activity. The PPARγ agonistic activity of KY-201, which was reported using human PPARγ in COS-1 cells (10), was re-examined with a transactivation assay using murine PPARγ in ST-2 cells because transactivation activity varies depending on gene and cell types. The affinity and maximal activation levels of KY-201 were 2 times lower than those of rosiglitazone. ST-2 cells can differentiate into osteoblasts and adipocytes (30, 31), and PPARγ agonists are known to promote adipocyte differentiation, resulting in a reduction in osteoblast differentiation (28, 29). The weak PPARγ partial agonistic activity of KY-201 suggests that KY-201 more weakly promotes adipocyte differentiation and reduces osteoblast differentiation than rosiglitazone in mesenchymal stem cells. In rat BMSCs, rosiglitazone markedly increased GPDH activity, an adipocyte marker enzyme, and reduced ALP activity, an osteoblast marker enzyme; however, the effects of KY-201 at higher concentrations were significantly weaker than those of rosiglitazone. The increasing effects of KY-201 on the expression of PPARγ2, C/EBPα, GPDH, lipoprotein lipase, adipocyte protein 2, and adiponectin, all biomarker genes of adipocytes (29, 32), were also weaker than those of rosiglitazone in rat BMSCs cells. These findings demonstrate that KY-201 partially activates PPARγ, unlike rosiglitazone, a full PPARγ agonist, resulting in fewer PPARγ-mediated adverse effects.

KY-201 activates human, but not rodent PPARα (ref. 10 and unpublished data), leading to hypocholesterolemic and body weight reducing effects in patients. PPARα agonists are known to have cholesterol- and TG-reducing effects, improve insulin sensitivity, and may also reduce body weight (33, 34). KY-201 increased hepatic Acy-CoA activities in hamsters and reduced plasma cholesterol levels in hamsters, beagles, and monkeys (ref. 10 and unpublished data). The multifaceted characteristics of KY-201, including weak PPARγ and PPARα agonistic activities and PTP1B inhibitory activities, may beneficially exert additive and/or syner-
gistic effects in the treatment of type 2 diabetic patients at risk of cardiovascular disease, osteoporosis, and obesity. The therapeutic potentiality of KY-201 could be further clarified in future studies using diabetic OVX rats or diabetic hamsters.

In conclusion, KY-201, a partial PPARα/γ agonist with PTP1B inhibitory activities, exhibits TG- and NEFA-reducing effects via insulin sensitization by the combination of PTP1B inhibitory activity and partial PPARγ agonistic activity; and it has fewer PPARγ-mediated adverse effects such as reductions in BMD as well as fluid retention, cardiac hypertrophy, and increases in body and adipose weights due to partial PPARγ activation. The combination of partial PPARγ agonistic activities and PTP1B inhibitory activities is suggested to be a useful and effective approach in the treatment of type 2 diabetic patients at high risk of osteoporosis as well as cardiovascular disease and obesity.

Conflicts of Interest

M.K., M.F., Y.I., T.K., and H.S. are employees of Kyoto Pharmaceutical Industries; E.H. and Y.Y. have no conflicts of interest.

References


